Role of PET Imaging in Adaptive Radiotherapy for Lymphoma

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Abstract

PET/CT is an essential part of modern radiotherapy treatment for patients with lymphoma. PET/CT can be used to adapt treatment algorithms in Hodgkin lymphoma, reserving consolidation radiotherapy for patients with residual FDG avidity after treatment with intensive chemotherapy such as escalated BEACOPP and limiting the need for radiotherapy for some patients with complete metabolic response on PET if radiotherapy may be associated with increased toxicity.

More importantly, PET/CT is now mandatory to define sites of initial disease for radiotherapy planning where smaller volumes are to be used rather than historical extended field treatments, such as mantle radiotherapy or even involved field radiotherapy. Involved node radiotherapy (INRT) treats only the initially involved nodes and is possible when the pretreatment PET/CT scan has been performed in the radiotherapy treatment position. Involved site radiotherapy (ISRT) builds in a margin for uncertainty when a pretreatment PET/CT is available, but has not been performed in the radiotherapy treatment position. Studies suggest that PET/CT changes radiotherapy volumes in approximately one third of patients by mapping the extent of initial disease better than using CT alone. PET/CT has also been used to adjust radiotherapy dose for patients who may be at increased risk of radioresistance, by virtue of residual FDG avidity post chemotherapy or patients with relapsed disease. This article will discuss the role of PET in selecting patients for radiotherapy treatment, its influence on the choice of target volume and radiotherapy dose and the practicalities of how PET/CT scanning is incorporated into the radiotherapy planning process. (250 words)

Introduction

Positron Emission Tomography (PET) combined with computed tomography (CT) has now become the standard imaging modality in lymphoma, with application in Hodgkin Lymphoma (HL), diffuse large B-Cell lymphoma (DLBCL) and follicular lymphomas (FL) using the tracer 2-deoxy-2-[18F]fluoro-D-glucose (FDG)[1]. While PET-CT can also be used for imaging other FDG-avid indolent non-Hodgkin's lymphomas (NHL), it is widely regarded as indispensable in the management of HL and high-grade NHL, where is used for staging and selection of therapy [2]. PET can be used during and after treatment to monitor response, using a 5-point scale based on the intensity of residual FDG uptake compared to reference regions of normal mediastinum and liver, referred to as Deauville score[3]. Response monitoring can predict the outcome of treatment[4] and more recently PET has been used to tailor treatment with adaptation to chemotherapy and sometimes selection of cases for radiotherapy based on interim and end of chemotherapy response.

In addition, the improved sensitivity and specificty of PET over structural imaging has resulted in PET playing an important role in modern radiotherapy (RT) planning. The information obtained from PET/CT provides accurate mapping of sites of disease involvement and enables the application of modern RT techniques in lymphoma, namely involved-node RT (INRT) and involved-site RT (ISRT) which reduce the risk of RT related toxicity significantly.

Radiotherapy treatment in lymphoma has been practiced successfully for decades and was the first curative treatment[5-7], however the use of radiotherapy has decreased and its role has changed as successful systemic treatments have been developed over time[8-10], in an attempt to improve outcome by reducing systemic relapse outside the initial sites. The use of combined modality approaches not only improved outcome but also allowed the reduction of the extent and dose of RT

with consequent reduction of late toxicity for lymphoma survivors. Several studies have examined whether RT could be omitted in HL patients achieving complete metabolic response to chemotherapy, but none have shown that RT can be omitted without an increase in relapse rates [11-14]. The need for radiotherapy is also dependent on the efficacy of the chemotherapy regimen and it has therefore, become necessary to adapt treatments in accordance with the choice of combined modality treatment (CMT).

In modern lymphoma treatment, radiotherapy is frequently used for consolidation purposes after chemotherapy, when there is no residual metabolically active disease on PET, although in many cases there is residual measurable disease. Information obtained from the baseline pre-chemotherapy PET/CT is therefore essential to define the RT target. In other cases, RT is given to control residual disease after chemotherapy in which case the "current" PET scan shows metabolically active disease. RT can also be used as the primary definitive treatment without prior chemotherapy in certain cases. In all these scenarios, PET/CT at various points in the course of treatment is the main stay for the definition of the radiotherapy target.

Hence the use of PET-adapted treatment in lymphoma can be considered in two settings: [A] PET adapted combined modality treatment i.e. role of PET in the choice and modification of treatment plan including decision to give RT, and [B] PET adapted radiotherapy i.e. the integration of PET into radiotherapy planning and the resulting modifications to treatment.

PET-adapted treatment in lymphoma

[A] PET adapted combined modality treatment

HL has excellent long-term survivorship, but with associated toxicity. Several trials have tested whether a good treatment response on PET could be used to select patients in whom to de-escalate

treatment in an attempt to reduce toxicity and/or intensify treatment in certain subgroups to improve survival.

The UK RAPID trial[13] investigated 602 patients with stage I or IIA HL, without mediastinal bulk, treated with three cycles of Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (ABVD) followed by response assessment with PET. Patients with a 'negative' PET3 scan, assessed as FDG uptake equal to or less than the normal mediastinum (Deauville score 1 and 2) were randomised to receive Involved Field Radiotherapy (IFRT) 30Gy or no further treatment. PET 'positive' patients underwent a fourth cycle of ABVD and IFRT.

A per protocol analysis showed a 3-year Progression Free Survival (PFS) for CMT of 97.1% (95% CI, 94.7 to 99.6) and 90.8% (95% CI, 86.6 to 94.7) for no further treatment, with a hazard ratio (HR) of 2.36, p = 0.02 in favor of CMT. Even in patients with good PET response, the omission of RT resulted in inferior progression free survival (PFS), confirming the need for RT to maintain a higher cure rate. However the outcome of the chemotherapy alone arm was still excellent, suggesting that for patients in whom RT may be associated with higher toxicity, omission of RT could be considered on an individualised risk-benefit assessment. Longer follow-up of overall survival (OS) is awaited as the reported results were based on a relatively small number of events and the long term toxicity data will be equally informative.

The H10[12] study, conducted in Europe by EORTC/LYSA/FIL groups, investigated the role of treatment adaptation based on interim PET after 2 cycles of ABVD chemotherapy in 1950 patients with stage I/II favourable (F) and unfavourable (UF) HL. The classification of F/UF was based on the established EORTC risk factors, commonly used in trials. Patients in each group were randomised to standard and experimental arms. In the standard arm, patients were treated without adaptation according to the PET result and all patients received ABVD (3 cycles for F and 4 cycles for UF disease respectively) + INRT. In the experimental arm, treatment was adapted based on the PET2 response. A 'negative'

PET scan, using the mediastinal threshold, as in RAPID, was used to assign complete metabolic response (Deauville 1, 2). Patients with negative PET scans in the experimental arm received a further cycle of ABVD (total 3) for F disease or 4 further cycles (total 6, i.e. 2 more than standard arm) in case of UF disease and RT was omitted. Patients with a 'positive' PET2 scan in the experimental arm received escalated treatment, with a further two cycles of BEACOPPesc (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone) followed by INRT. The outcome was compared between experimental and standard arms by PET2 group.

After an interim analysis[14], randomisation to no RT arm was stopped, for both favourable and unfavourable patients, as the analysis found higher incidence of relapse in the no RT arm and concluded that treatment without RT was unlikely to be non-inferior to CMT. For the RT comparison, final results reported five-year intention to treat PFS rates in the group with favourable disease of 99% (95% CI, 95.9 to 99.7) for patients receiving CMT versus 87.1% (95% CI, 82.1 to 90.8) for patients receiving chemotherapy only, HR = 15.8 (95% CI, 3.8 to 66.1) . In the group with unfavourable disease 5y-PFS was 92.1% (95% CI, 88.0 to 94.8) for patients receiving CMT versus 89.6% (95% CI, 85.5 to 92.6) for patients receiving chemotherapy only respectively, HR = 1.45 (95% CI, 0.8 to 2.5) in favor of CMT. Notably, the effect of radiotherapy was more pronounced in the favourable group. It is also important to note that in the unfavourable group where there was a smaller difference between the no RT and CMT arms, the chemotherapy duration was increased by further 2 cycles.

Results for the patients in the PET-positive group showed PET directed escalation to BEACOPPesc + INRT resulted in an improved 5y-PFS of 90.6% (95% CI, 84.7 to 94.3) when compared to treatment with ABVD + INRT of 77.4% (95% CI, 70.4 to 82.9), HR 0.42 (95% CI 0.23 to 0.74, p = 0.002) in favour of BEACOPPesc and INRT. In summary, the study showed that intensifying chemotherapy in PET

positive patients significantly improved PFS, but omission of RT in PET negative patients increased relapse, mainly in patients with favourable disease.

The RATHL[15] trial investigated the possibility to reduce chemotherapy based toxicity, related to bleomycin in the ABVD combination in 1214 patients with advanced HL. Treatment was adapted based on PET response after two cycles of ABVD. PET negative patients, using a threshold of FDG uptake lower than or equal to normal liver (Deauville 1-3) were randomised to receive standard treatment with 4 further cycles of ABVD (total 6) or to receive de-escalated treatment with a further four cycles of AVD, omitting bleomycin. Patients with a positive PET2 scan received escalated treatment with BEACOPP chemotherapy but no radiotherapy. There was no significant difference in 3y PFS 84.4% (95% CI,80.7 to 87.5) and 85.7% (95% CI, 82.1 to 88.6) for patients with PET negative scans who received AVD compared to ABVD respectively but lower toxicities were experienced by patients who received AVD. 3yPFS for patients with PET positive scans was 67.5%.

The HD15[16] trial, conducted by the German Hodgkin Study Group, investigated 2126 patients with advanced stage HL using BEACOPP as standard treatment, comparing three different combinations - 8 cycles of escalated BEACOPP, 6 cycles of escalated BEACOPP and 8 cycles of BEACOPP 14. PET imaging on completion of chemotherapy was performed in patients with residual soft tissue masses of 2.5cm or above and used to select patients with a positive PET for consolidation radiotherapy. The radiotherapy arm was not randomized, but showed a forty-eight-month progression-free survival of 86.2% in comparison to patients with PET negative scans of 92.6% (95% CI for difference 0.9-12.0, log-rank p=0.022). This outcome was much better than historical controls with PET positive disease at the end of chemotherapy and suggests that PET-based RT after BEACOPP improves outcome of this high risk group to a level comparable to the PET negative group. The chemotherapy randomisation resulted in favouring 6 cycles of BEACOPPesc. The authors' concluded that six cycles

of BEACOPP followed by PET directed RT were less toxic than eight of BEACOPP. This is one of the few studies to look at PET directed escalation of treatment with radiotherapy in HL.

These studies established PET as a useful tool to help adapt treatment algorithms based on metabolic response to improve patient outcome and reduce treatment burden.

[B] PET-based Radiotherapy

PET/CT is essential for modern lymphoma RT to confirm the stage of disease and the appropriate use of RT. PET/CT allows the treating radiation oncologist to map the extent of disease, accurately define the RT target and help with the choice of RT dose, depending on the degree of response to chemotherapy.

<u>PET for accurate staging before RT</u>

RT is a local treatment modality and where it is used as the sole treatment, it is important to ensure that staging is accurate and all sites of involvement can be covered in the RT volume to be irradiated. One example where staging PET makes a significant impact is in the case of early stage FL where studies have shown upstaging in 30-50%[17,18]. Upstaging may result in change of treatment from potentially curative RT to more systemic approaches aimed at disease control rather than cure. A recent international study has confirmed an improved outcome of PET-staged FL after RT compared to historical series based on conventional staging[19].

PET adapted Radiotherapy

Modern RT for lymphoma treats smaller volumes and uses lower doses as systemic treatment is frequently used before RT and the primary role of RT in this situation is the local control of sites of involvement which are the most common site of recurrence after chemotherapy. These changes are reliant on improved imaging in defining sites of involvement. On the other hand, where RT is given as the sole modality (see below), it is important to ensure that all sites of disease are included to achieve disease control. The important role PET imaging plays in defining RT target and dose is discussed below.

Role of PET in RT target definition:

The extent of RT target volume depends on accurate mapping of sites of disease involvement, understanding of the disease natural history and the context in which RT is used i.e. single modality, consolidation as part of combined modality treatment, salvage for incomplete response to chemotherapy or palliative radiotherapy.

In CMT approaches, systemic chemotherapy very effectively treats microscopic disease covered in the originally extended RT field treatments of the past (e.g. Mantle or total nodal irradiation), allowing the reduction of RT target to originally involved sites which are the most common site of recurrence following systemic therapy[20,21]. In these cases there is no need to cover non-involved sites on a prophylactic basis [12,14]. On the other hand, radiotherapy is the treatment of choice as a single modality for some lymphomas, for example localised low-grade NHL (follicular lymphomas and marginal zone lymphomas both nodal and extra nodal), localised nodular lymphocyte predominant HL and when chemotherapy is not suitable for some patients with high-grade lymphoma. In these cases including areas with the highest risk of harbouring microscopic disease

should be considered and weighed up against the expected side effects to maximise cure with the least toxicity possible. Accurate disease mapping on PET/CT is invaluable in these situations.
In addition to reduction of volume, the dose of radiotherapy has successfully been refined and reduced through a number of RCTs[22]: 20Gy in favorable early-stage Hodgkin's lymphoma[22,23], 24Gy in Follicular and Marginal Zone lymphoma and 30Gy in Diffuse Large B-cell lymphoma[24,25].

The use of limited radiotherapy to treat only sites of original disease has led to the emergence of two key modern-day lymphoma radiotherapy concepts: involved-node and involved site radiotherapy.

Involved node radiotherapy (INRT) delivers radiotherapy to the initial involved nodes only. The RT Clinical Target Volume generated (CTV) during the planning process is defined as the volume that encompasses the involved nodes only not a nodal chain or lymphatic region. INRT does not take into account any form of treatment for microscopic disease. INRT is only possible if optimal imaging is available and strict criteria are followed as suggested by Girinsky et al: the patient must be examined by a radiation oncologist; the patient must have a pre- and post-chemotherapy PET/CT, and the PET/CT must be performed in the treatment position[26].

In most clinical practices, pre-treatment PET/CT scans are usually done according to diagnostic imaging protocols and not in the radiotherapy treatment position or on a flat table top, as imaging often takes place before the patient's treatment plan has been formulated. Repeating the PET for radiotherapy treatment planning would require additional radiation exposure and therefore not usually done. The lack of a pre-chemotherapy planning PET in the treatment position introduces an element of uncertainty. Difference in patient positioning between the pre-treatment imaging and the radiotherapy planning imaging can cause uncertainty about the position of involved nodes and

which nodes should be treated, especially as after chemotherapy, the soft tissue mass(es) may shrink or completely disappear (Figure 1) [27] .

Whenever possible the ideal scenario is to have a pre-chemotherapy PET scan in the treatment position (with flat bed couch, immobilisation devices and skin markers) in which case it can be accurately co-registered with the post chemotherapy radiotherapy planning scan, allowing direct overlay of the two scans and accurate delineation of target volume[2]. If RT is delivered during deep inspiration breath hold (DIBH) which is increasingly common in mediastinal RT to remove the effect of respiratory motion and displace the heart and lung away from the mediastinal target, then ideally the separate DIBH views should also be acquired during diagnostic PET to enable accurate co-registration. However, PET scans acquired in different positions will not allow accurate co-registration and a certain amount of transcription must take place to delineate the correct nodes, in which case the ISRT principle, discussed below, is better suited.

The addition of optimally performed PET to the radiotherapy planning of INRT is vital if the efficacy of treatment is to be maintained as has been shown in previous studies. One study compared target volumes defined by CT versus PET in 30 patients. 36% of patients had nodes pinpointed on PET that was not seen on CT[28]. In a planning study for HL patients treated in the H10 trial, 135 patients who underwent INRT were independently planned using CT alone or CT and PET information. The addition of PET imaging resulted in finding at least one additional node in a striking 70.4% (95% CI, 61.9 to 77.9) of patients and one additional nodal group in 40.7% (95% CI, 32.4 to 49.5) of patients[29] confirming that INRT is not safe without using PET/CT as the imaging tool for planning. Retrospective studies investigating the effect of adding PET also confirm that approximately 30% of radiotherapy volumes change with the addition of PET to CT for planning. Therefore INRT cannot be reliably delivered to patients without 1) pre-chemotherapy PET, 2) PET in the radiotherapy treatment position.

It is important to note that in situations such as localised NLPHL or low grade NHL and other circumstances where radiotherapy is used as the primary/ sole treatment modality that areas at highest risk of microscopic disease must be considered and treated to ensure disease control[20].

To help compensate for difficulties delivering INRT, an adapted form of nodal radiotherapy has been developed by the International Lymphoma Radiation Therapy Group (ILROG). Involved Site Radiotherapy (ISRT) includes the concept behind INRT but builds in a margin for uncertainty to account for the lack of pre-treatment PET in the RT treatment position and changes in patient or disease anatomy after chemotherapy[20]. To maintain a smaller radiation field (compared to historical extended field RT), a pre-treatment PET is still required to ensure that all initial disease sites are covered adequately. A clinically-judged margin of uncertainty is added to the involved nodes to create a larger CTV which will account for the lack of a PET matched in position to the post-chemotherapy planning scan. With ISRT it is recommended that the CTV is adapted according to clinical judgment and the best available imaging based on the quality of the imaging, the interval change in volume/s, patterns of spread, potential subclinical spread and adjacent (normal) organ at risk constraints.

Hence to reduce volumes typically used in involved Field Radiotherapy, a pre-treatment PET in the treatment position must be available and co-registered with the CT planning scan for INRT. Lacking this, ISRT is an option that accounts for the lack of a co-registered PET. If there is no pre-treatment PET available, accurate treatment with either INRT or ISRT is not possible. PET is therefore invaluable to modern lymphoma radiotherapy.

PET-adapted RT Dose

Radiotherapy given after chemotherapy has been shown to improve local control and progression-free survival even after complete metabolic response on PET (EORTC H10[12], and RAPID[13]). Radiotherapy doses required to control microscopic disease after CMR have been established for many lymphoma types. For example, for early stage HL without risk factors 20Gy is sufficient while for early stage HL with risk factors, 30 Gy is required for ABVD treated patients [30]. For DLBCL, a randomised controlled trial demonstrated that 30 Gy was equivalent to treating with higher doses and for low grade lymphoma (FL & marginal zone lymphoma) 24Gy was equivalent to treating with 40 Gy[30] and in another study 24Gy was superior to 4Gy, establishing 24 Gy as the dose of choice for low grade lymphoma.

However for patients who have residual FDG activity on PET, there has not been any definitive studies determining the optimal RT dose to achieve the best outcome. Expert opinion and many publications tend to suggest that a higher dose of RT is required for residual lymphoma. In our opinion, this is justified policy for two reasons - the potential for a dose-volume effect and the potential for the presence of a degree of radio-resistance in the context of chemotherapy resistance.

The German Hodgkin Study group randomised HD10 study showed that in early stage HL, 20 Gy was equivalent to 30Gy if there were no risk factors, while their HD11 study showed that 20 Gy was inferior to 30Gy in patients with risk factors (including bulk) in ABVD treated patients, raising the possibility of a relationship between disease volume/burden and dose required, at least in ABVD-treated patients. Other studies also used the presence of a residual soft tissue mass as an indication for giving a higher dose boost to the mass (e.g. EORTC H9 [22]). Several retrospective studies have showed that in routine clinical practice, higher doses tend to be given to residual FDG-avid areas (e.g. Sher et al 2009 treated patients with CMR with 30Gy and patients with partial metabolic

response with 36Gy [31]). Similar evidence exists for DLBCL. Local control data for RT shows lower local control for PET positive compared to PET negative disease, suggesting that there is a degree of radioresistance in the context of chemoresistance and the need for higher doses[32-34].

This can be seen in HL patients treated with ABVD, where 70% of the PET positive patients were free of disease at two years (versus 97% who were PET negative). A failure rate of 30% was seen despite the higher dose of 36Gy[31]. In another study in HL patients treated with STANFORD-V regimen, 67% of patients with FDG uptake post chemotherapy relapsed compared to 4% of PET negative patients. All relapses in this population were in the radiation field [35]. The German HD 15 study used 30 Gy to treat FDG-avid patients with consolidation radiotherapy after escBEACOPP. Although the outcome of patients with PET positive and negative scans were similar suggesting that consolidation RT counteracted (some of) the worse prognosis of PET positive disease, the pattern of relapse was similar with 25% of patients recurring exclusively outside of the radiation field and 39% of failures exclusively within the field[36]. The higher in-field recurrence rate in patients with PET positive scans is also seen in the DLBCL population. In a retrospective study using cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) +/- rituximab and radiotherapy to the FDG-avid sites to 36 Gy, although only one patient recurred solely in the radiation field, 80% of patients with recurrent disease had sites that included an in-field site[37]. 65% of the group with PET positive scans however remained disease free, suggesting there is a role for radiotherapy to avert salvage therapy.

Hence whilst the pattern of relapse in patients who complete chemotherapy and have a positive PET scan afterwards is not exclusively seen within the radiotherapy treatment field but most are, raising the possibility that the dose to FDG-avid areas is not sufficient to eradicate disease. The high percentage of patients who remain disease free after consolidation radiotherapy would indicate that this modality is a suitable alternative to immediate salvage treatment for most patients.

It is unlikely that randomised clinical trials addressing RT dose escalation for PET positive residual disease will be feasible, but the above data raise the question of whether higher doses are required to achieve better outcomes.

Modern radiotherapy technology such as intensity modulated radiotherapy (IMRT) allows better shaping and contouring of the radiotherapy dose distribution and multiple dose levels within the treated volume. This allows escalation of dose to select areas thought to contain residual disease after chemotherapy. A patient with residual FDG uptake seen on an end of chemotherapy treatment scan can be treated with 30Gy to the components demonstrating complete metabolic response and a higher integrated dose (36-45Gy[38]) can be given to the residual FDG-avid components. This concept is known as "integrated boost" or "dose painting" and has many advantages including delivering multiple dose levels within same plan and same treatment session with no change in patient nor machine parameters, as opposed to a separate small volume boost delivered subsequently to the baseline dose. The concept of integrated boost is advocated in the latest guidance from the International Lymphoma Radiation Oncology Group (ILROG) for relapsed or refractory HL[38]. This is obviously only possible with PET/CT information available both before chemotherapy (defining all sites of involvement) and after chemotherapy (defining sites of residual FDG-avid abnormalities). In this case multiple fusions of diagnostic PET/CT scans with the planning CT are needed with different volumes (e.g. CTV-30Gy and CTV-40Gy) defined using different fusions. Where possible, performing a dedicated PET/CT for RT planning would be advantageous to accurately define the high dose CTV and escalate dose safely.

Technical aspects of PET imaging and RT Planning:

Registration and image fusion

Most pre-treatment PET imaging is performed with the patients arms up and on a curved couch top before any decision is made the treatment plan and sometimes before the haemato-oncology team is involved. A decision must be made whether it is worthwhile then to perform a second PET/CT scan which has additional radiation and cost. When treating FDG- avid disease areas (e.g. early stage NLPHL and FL or localised residual disease or relapsed disease) it is worthwhile to perform a proper PET/CT in the treatment position for the purpose of RT planning, sometimes referred to as PET/CT simulation.

The use of ISRT helps with volume delineation allowing the radiation oncologist to use his/her clinical judgement to account for changes in position and changes in anatomy after chemotherapy, but it is recommended that the pre-treatment PET is fused with the radiotherapy planning scan. Importing the PET image is easily done, the difficulty comes with registering the PET and CT components. Two forms of image registration exist: rigid registration uses bony structures to match and deformable registration uses an algorithm to reduce the geographical differences of the different image sets, in a region of interest[39]. Deformable registration of the PET/CT data set has been shown to improve the match with the planning CT[40]. This should be reviewed carefully with all imaging when delineating structures.

Treatment position and PET

The position of the initial pre-chemotherapy PET can be difficult to get right if the patient has not had prior imaging which shows the distribution of the disease to ensure the correct positioning. The arm position and type of immobilization will differ according to distribution of disease and the type

of radiotherapy technique. As radiotherapy treatments become increasingly more complex and more accurate treatment positioning is required e.g. when deep inspiratory breath hold is used for treatment, the pre-treatment PET scan positioning becomes even more important.

One study trying to account for differences in positioning when using a diagnostic instead of a pretreatment PET acquired in the RT treatment position for neck RT compared the difference in CTV outlined using the two scans, essentially ISRT and INRT[41]. A mean addition to the superior aspect of the CTV of 10mm and inferior aspect of 18mm was needed to encompass all PET active areas using the diagnostic PET scan. Delineation was carried out using side by side for the diagnostic PET and a rigid co-registered PET in the treatment position. The treatment position PET co-registration demonstrated better intra and inter-observer agreement between radiation oncologists. This study was limited to neck RT only.

Respiration-induced motion

Respiration has long caused issues with radiotherapy planning in the thorax, due to respiratory motion movement of the target volume and adjacent organs resulting in the potential to miss or underdose tumour and overdose normal tissue. Compensation for this movement was initially implemented by increasing the CTV margin to include respiratory motion, thereby creating an "Internal Target Volume". Two methods can be used to reduce the consequences of increasing normal tissue irradiation with a larger CTV. These are the use of 4D scanning, which images the patient in all phases of respiration (typically divided into ten gates) and allows delineation of the target volume across ten gates to ensure the complete tumor/ structure is treated. This allows a smaller 'custom' margin to be applied, thus shrinking the ITV, or at the very least, adapting it for individual patients. In mediastinal lymphoma, a second method to reduce the TV by treating during a deep inspiratory breath hold (DIBH) has become popular. With DIBH, a patient is scanned and treated whilst holding a deep breath. Patients need to be able to hold their breath in deep

inspiration for 20-30 seconds at a time and to do so in a consistent manner. The degree of deep breath is recorded on the RT planning scan and is replicated during treatment. A method to ensure achieving the same level of deep breath is used and is usually based on a chest-wall surface monitoring system on the treatment machine with the facility to interrupt treatment if the chest wall moves out of a pre-determined tolerance. This has the advantage that the thorax is not moving, and an ITV is not needed with a resultant smaller CTV. 4D CT and DIBH reduces the dose to normal tissues [42-44]. The effect of breathing is not just limited to radiotherapy but to the acquisition of the PET imaging. Motion causes a blurring of the PET image and an increase in inhomogeneity. Recent advances in PET imaging with the use of DIBH PET capture in the mediastinum have resulted in PET images where the TV is smaller and can be fused more precisely with the planning scan[45] reducing the uncertainty resulting from fusing 2 scans in different respiratory phases. The reduction in inhomogeneity will have an impact on the SUV of mediastinal structures, which may need to be taken into account when delineating positive node/s if using a threshold based approach.

Summary

The use of PET in the treatment of lymphoma has become the gold standard for initial staging. Adaptive treatment algorithms based on the response on PET after two or three cycles of chemotherapy have been useful in escalating at-risk patient populations and limiting the need for radiotherapy in patients in whom RT may be associated with higher toxicity. Modern radiotherapy planning depends heavily on PET imaging where studies have shown that PET information guides patient selection, changes target radiation volume in a significant proportion and is valuable in dose selection.

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Figure legends

Figure 1A

Axial fused PET/CT image of mediastinal lymphoma prior to chemotherapy

Figure 1B

Axial fused PET/CT image after chemotherapy shows reduction in size and change in shape of the mass which now has no significant FDG uptake. The planning CT will need to be co-registered to the pretreatment PET/CT or visually compared to ensure that all areas of original disease (the pre chemotherapy GTV) are included in the post chemotherapy target volume.